IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	F.C. Prats
Art Unit	:	1651
Applicant	:	Bruce Joseph Roser
Serial No.	:	08/875,796
Filed	:	October 30, 1998
For	:	Dried Blood Factor Compositions Comprising Trehalose

DECLARATION OF FRANCIS E. PRESTON UNDER 37 CFR 1.132

I, Francis E. Preston, hereby declare that:

My C.V. is attached.

I have read and understood the subject application, and the Office Action dated December 13, 2001. I have also reviewed the following references:

Curtis *et al.* (U.S. Patent No. 5,576,291, issued November 19, 1996)

Livesey *et al.* (U.S. Patent No. 5,364,756, issued November 15, 1994)

AND, being thus duly qualified, do further declare:

Factor VIII is a critical component in the human blood clotting process. Factor VIII deficiencies are responsible for haemophilia A which is a blood clotting disease afflicting a significant number of people. Through the administration of Factor VIII to those with haemophilia A, it is possible to minimize disability and to prolong life.

Unfortunately, obtaining sufficient quantities of Factor VIII to meet the demand for treating haemophilia patients has been very difficult. Factor VIII is present in low concentrations in blood plasma making it difficult to purify large quantities of Factor VIII. Also, plasma-derived blood factors carry a risk of transmitting viruses and other infectious agents.

Although the gene which encodes Factor VIII was identified in the mid-1980's, technical problems have hindered the ability to produce sufficient quantities of therapeutic preparations of

recombinant Factor VIII. One of the primary technical challenges is to stabilize the highly labile Factor VIII. Factor VIII is an extremely delicate protein, regardless of whether it is produced recombinantly or purified from plasma. Native Factor VIII contains multiple enzymatic cleavage sites making it highly susceptible to degradation. In the past, degradation of Factor VIII preparations has been avoided or minimized using albumin as a stabilizing agent.

Factor VIII purified from plasma necessarily contains albumin. Although the presence of albumin increases the chances for contamination with pathogens, albumin has been left in Factor VIII compositions purified from plasma because albumin was believed to be necessary to stabilize Factor VIII. Furthermore, until recently, a stabilizing amount of albumin was actually added to all therapeutic recombinant Factor VIII preparations. This practice has continued despite the potential health risks associated with albumin.

For years, it has been well known to those skilled in the art that Factor VIII, which is a large protein having over 2000 amino acids, is highly susceptible to degradation. In the human body, enzymes act on native Factor VIII during the clotting process. As the result of a complicated enzymatic conversion process, Factor VIII is transformed *in* vivo into a heterotrimer known as activated Factor VIII (Factor VIIIa). Specifically, proleolytic processing by thrombin results in the formation of Factor VIIIa which is, itself, a cofactor in the activation of Factor X by Factor IXa. Native Factor VIII is not a cofactor in the conversion of Factor X.

Thus, activated Factor VIII is a different chemical entity than Factor VIII. Activated Factor VIII has chemical, physical and physiological properties which all differ from Factor VIII. The scientific literature is replete with references to Factor VIII as well as to Factor VIIIa. The skilled artisan, in 1995, would be fully aware of the different nature of these compounds. The skilled artisan would also have been fully aware of the delicate nature of Factor VIII and the standard practice of stabilizing Factor VIII with albumin. At the time of the subject invention, those skilled in the art would recognize that "native Factor VIII" does not refer to activated Factor VIII.

Unlike Factor VIII, activated Factor VIII is not produced recombinantly. Rather, activated Factor VIII is produced by subjecting Factor VIII to proteolytic cleavage. This can be done, for example, by the process described by Curtis *et al.*

The Curtis *et al.* patent pertains to the administration of activated Factor VIII to treat a

particular complication of haemophilia. Curtis *et al.* intentionally proteolytically cleaves Factor VIII to obtain activated Factor VIII. This, of course, does not provide the skilled artisan with any information regarding the stability of Factor VIII, since the Factor VIII was purposefully degraded. I have not identified any disclosure in the Curtis *et al.* reference which would teach or suggest that native Factor VIII can be stabilized by trehalose in the absence of added albumin.

Finally, from my review of the Livesey *et al.* patent I again find no disclosure which would teach or suggest to a person skilled in this art that highly labile Factor VIII could be stabilized by trehalose in the absence of added albumin.

The undersigned declares further that all statements made herein of his own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the Application or any Patent issuing thereon.

Further declarant sayeth naught

Signed: 

Date: 24.5.02

CURRICULUM VITAE

PROFESSOR FRANCIS ERIC PRESTON

Emeritus Professor of Haematology

MD, FRCP, FRC.Path

FEP/SLR
June 2002

Name: Francis Eric PRESTON

Home Address: Clifton House
7 Broomhall Road
SHEFFIELD S10 2DN

Professional Address: Royal Hallamshire Hospital
Department of Haematology
Glossop Road, SHEFFIELD S10 2JF

Date of Birth: 26 January 1935

Specialty: Haematology

Degrees: MB ChB Liverpool 1963

MD (Liverpool) 1970
Jejunal Disaccharidases-Their Histopathological and Clinical Significance

Postgraduate Qualifications: MRCPath
Royal College of Pathologists 1970

FRCPath
Royal College of Pathologists 1982

MRCP (By election, with citation)
Royal College of Physicians,
London 1987:

FRCP
Royal College of Physicians,
London 1992

Current and Past Positions:

Professor of Haematology
University Department of Haematology
Royal Hallamshire Hospital
Glossop Road, SHEFFIELD
1986-

Director
Sheffield Comprehensive Care Haemophilia Centre
Royal Hallamshire Hospital
Glossop Road, SHEFFIELD
1973-2000

Consultant Haematologist
Royal Hallamshire Hospital
Glossop Road, SHEFFIELD
1973-

INTERNATIONAL APPOINTMENTS AND RESPONSIBILITIES

World Health Organisation

Director
WHO Collaborating Centre for the Diagnosis and Comprehensive Care of Patients with Bleeding and Clotting Disorders. This is only one of two such WHO-designated centres worldwide. 1994-2000

Director
WHO International External Quality Assessment Scheme in Blood Coagulation for Developing Countries (WHO IEQAS) 1994-current

Chairman
Co-ordinating Group of the WHO International External Quality Assessment Scheme (IEQAS) in Blood Coagulation 1997-current

International Society on Thrombosis and Haemostasis (ISTH)

Chairman
SSC Scientific Subcommittee on Control of Anticoagulation
1997-2000

Co-Chairman
SSC Scientific Subcommittee on Control of Anticoagulation
1996-current

Chairman
Working Party on Near Patient Testing and Self-Management of Oral Anticoagulant Control
1999-current

Member
Scientific and Standardization (SSC) Committee
1994-current

Member
SSC Working Group on Coagulation Standards
1995-current

Member
ISTH Scientific and Standardization Committee (SSC) Representative for WHO for the education and training in laboratory techniques for participants from developing countries

Member
International Advisory Committee for the XVIIth Congress of the International Society on Thrombosis and Haemostasis (ISTH), Washington, United States - 1999

Member
International Advisory Board for the XVIII Congress of the International Society on Thrombosis and Haemostasis (ISTH), Paris, July 6-12, 2001

World Federation of Haemophilia (WFH)

Director
WFH External Quality Assessment Scheme for Haemophilia Centres in Developing Countries 1993-current

Co-Chairman
WFH Laboratory Science Committee 1996-current

Director
WFH designated International Haemophilia Training Centre 1994-2000

Chairman
World Federation of Hemophilia Working Party on Chronic Liver Disease in Haemophilia
1990-1994

Member
Medical Advisory Panel 1988-1995

Member
WFH Visiting Faculty on Haemostasis and Thrombosis
to 1) Tianjin, China (1993) and 2) Jakarta, Indonesia (1994)

The British Council

Formal British Council link established between Sheffield and Recife, NE Brazil 1989-1994

Personally responsible for developing clinical and laboratory services in respect of Haemostasis and Thrombosis (including Haemophilia) 1989-1994

International Society of Haematology (ISH)

Member
Nomenclature Terminology, Quantity and Units Committee
1994-current

Member
Standing Committee on Education and Training
1996-current

European Prospective Cohort on Thrombosis (EPCOT)
This is an EC-funded European Collaborative Study in Familial Thrombophilia

Member
Steering Committee
1994-current

European Haematology Association

Member
1996-current

Stroke Prevention in Reversible Ischaemia Trial

Member
Advisory Committee of the European and Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT)
1997-current

European Network on Oral Anticoagulant Treatment (ENAT)

Member
Board of ENAT
1997-current

External Examiner in Haematology for Master of Pathology Examination

University of Malaya, Kuala Lumpur
1988, 1992, 1995, 1999-2002

External Academic Appointments Assessor for Department of Pathology

University of Malaya, Kuala Lumpur
1988-1996
1999-2002

European Thrombosis Research Organisation (ETRO)

Member
Council of ETRO 1991-1994

Head
Elected ETRO Laboratory
1988-current

Elected UK Representative 1991-1994
Re-elected 1994-current

Member
Working Party on Familial Thrombotic Disorders

NATIONAL APPOINTMENTS AND RESPONSIBILITIES

Department of Health

Adviser to the Department of Health in respect of research requirements for individuals infected with chronic hepatitis C virus
1997

Department of Trade and Industry

Invited Member
Medical and Research Laboratories Interest Group (MERLIN)
1998

UK National External Quality Assessment Scheme (UK NEQAS)

Chairman
UK NEQAS for Blood Coagulation
1991-1992

Director
UK NEQAS Scheme for Blood Coagulation
1992-current

British Society for Haematology (BSH)

President
1995/96

Elected Committee Member
1984-1987

Committee Member (As representative of the British Society for Haematology (BSHT)
1989-1992

Member
Haemostasis and Thrombosis Task Force
1985-current

Member
British Committee for Standardisation in Haematology
1985-1988

Member
Subcommittee on European Matters
1996-current

British Society for Haemostasis and Thrombosis

President
1988-1989

Honorary Secretary
1983-1988

Committee Member
1982-1990

British Atherosclerosis Society
(Formerly MRC Atherosclerosis Discussion Group)

Member
1997-current

Royal College of Pathologists

Elected Fellow
1982

Member
Haemostasis Subcommittee of the Standing Advisory Committee on Haematology
1987-1991

Member
Standing Advisory Committee on Haematology
1991-1994

Member
Panel of Examiners for Haematology
1987-current

College Assessor in Coagulation and Haemophilia

Member
Visiting Teaching Group to Jeddah, Saudi Arabia 1996

Association of Clinical Pathologists

Member
1972-

British Heart Foundation

Member
Research Funds Committee 1988-1991

UK Haemophilia Society

Member
Medical Advisory Board
1989-current

UK Haemophilia Organisation

Member
UK Haemophilia Reference Centre Directors Organisation

Chairman
Committee of the Working Party on Congenital Platelet Disorders

Chairman
Chronic Liver Disease in Haemophilia Working Party
1990-1999

Member
Haemophilia Reference Centre Directors AIDS Group

Member
Factor VIII Inhibitor Working Party
1995-current

Principal Editor

Platelets Journal -(1989)

Editorial Boards

Member
Thrombosis and Haemostasis
1998-2004

Member
Blood Coagulation and Fibrinolysis Journal
1989-current

Member
Haemophilia Journal
1994-current

Member
Hemophilia Forum
1997-current

Member
The Hematology Journal
1999-

Review Editor

International Monitor of Hemophilia
1993-current

University of Sheffield

Member
Faculty Board

Member
Fourth Year Teaching Committee

European Community (EC) Representative for the Department of Haematology

Head of Section of Haematology
1996-2000

Member
Division of Molecular and Genetic Medicine Strategy & Planning Task Group

Trent Regional Health Authority

Member
Ad hoc Committee on AIDS

Member
Blood Borne Viruses Group

Member
Genetics Review Group

Sheffield Health Authority

Member
Advisory and Monitoring Group (AIDS and HIV)

Sheffield Teaching Hospitals
Royal Hallamshire Hospital, Sheffield

Member
AIDS Working Party

External Examiner for PhD/MD Theses

Universities of Nottingham, Southampton, London
Bath, Leeds, Aberdeen, Glasgow and Manchester

External Examiner for MB.BS

University of London Collegiate Committee of Examiners for examinations in clinical studies and related sciences for the M.B., B.S. Degrees

United Medical & Dental Schools of Guy's and and St Thomas's Hospitals, London

Numerous Publications available upon request.